

## PATENT ABSTRACTS OF JAPAN

(11)Publication number :

11-349451

(43)Date of publication of application : 21.12.1999

Date X

(51)Int.Cl.

A61K 7/06  
A61K 31/505  
// C07D239/50

(21)Application number : 10-158782

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(22)Date of filing : 08.06.1998

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MORIOKA SUSUMU

HORIE TARO

OKAJIMA TAKAKO

## (54) HAIR GROWER

## (57)Abstract:

PROBLEM TO BE SOLVED: To obtain a hair grower by including a specific amount of a volatile solvent, water, a pH adjustor and minoxidil so as to be excellent in the selective absorbability of the minoxidil into the hair papillae when administered to the scalp while securing the preservability of the minoxidil.

SOLUTION: This hair grower is obtained by including (A) pref. 50-99 v/v% of a volatile solvent such as ethyl alcohol, (B) water, (C) a pH adjustor such as phosphoric acid and (D) pref. 0.1-5 wt.% of minoxidil, and pref. further at least one kind of ingredient selected from 2-8C polyhydric alcohols, polyethylene glycol and fatty acid esters. It is preferable that this hair grower has  $\leq$ pH 4.8 when diluted ten-fold with purified water before applied to the skin; therefore the amount of the ingredient C to be formulated is pref. set at 0.01-5 wt.% based on the final hair grower.

## LEGAL STATUS

[Date of request for examination]

[Date of sending the examiner's decision of rejection]

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DETAILED DESCRIPTION

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[Detailed Description of the Invention]

[0001]

[Industrial Application] This invention relates to the hair restorer excellent in the preservation stability of the minoxidil, and the alternative absorptivity to woolen hair papilla.

[0002]

[Description of the Prior Art] The minoxidil calls a chemical name 6-(1-piperidiny)-2 and 4-pyrimidine diamine-3-oxide, and the adaptation as a hair restorer is stated to U.S. Pat. No. 4,139,619. Moreover, by prescribing the minoxidil for the patient as lotions or gel, terminal-hair-izing of pubes and production of downy hair are promoted, and it is known that the bald head of a head will improve.

[0003] Generally, the so-called partial prescribing [ for the patient ]-a medicine method make hair-fostering components, such as minoxidil, arrive at the purpose part via the scalp is used widely, and various hair restorers are developed.

[0004] The fundamental engine performance for which the hair restorer which blended the minoxidil is asked is excelling in the absorptivity of the minoxidil from the scalp. Therefore, it is considered to be the need to add the component (absorption promotion component) which generally has absorption promotion ability, and to raise absorption of the minoxidil.

[0005]

[Problem(s) to be Solved by the Invention] However, since many of conventional absorption promotion components are oily components, such as myristic-acid isopropyl, the hair restorer which blended this tends to spoil a feeling of use, such as being easy to be sticky etc., and has a problem in the viewpoint of salability. Moreover, since it rides on a blood flow and shifts to the whole body, while absorptivity of minoxidil which permeated this appearance through keratin improves in the hair restorer using the conventional absorption promotion component, it is difficult for it, although an oily absorption promotion component has the effectiveness of making the minoxidil permeating into the skin through a horny layer to the scalp to make the minoxidil pile up.

[0006] Moreover, generally, woolen growth is controlled by hair papilla of a hair bulb, and it is required to make the minoxidil arrive at the part concerned efficiently in order to acquire the higher hair-fostering effectiveness. this invention persons found that it was desirable that it is 4.8 or less pH at least below the acescence for the absorptivity and the permeability to hair papilla in the research process of the absorptivity from the scalp of the minoxidil.

[0007] On the other hand, as for the minoxidil, the inclination becomes strong, when it is an unstable drug and especially pH comes below the acescence into solutions, such as a lotion. Therefore, as for pH of a hair restorer, from a viewpoint of the preservation stability of the minoxidil in a solution, it is desirable that it is five or more.

[0008] Therefore, while excelling in the absorption efficiency of the minoxidil which reaches the hair papilla of a hair bulb, in order to offer the hair restorer which can be satisfied also in preservation stability, it is required to design a hair restorer with which it is at the preservation and use time, and pH becomes respectively suitable by the device like pharmaceutical preparation.

[0009]

[Means for Solving the Problem] this invention persons are combining the volatile organic solvent more than the amount of specification, water, and a pH regulator, and completed a header and this invention for this technical problem being solvable.

[0010] That is, this inventions are 50 to volatile solvent 99 capacity (V/V) %, water, a pH regulator, and a hair restorer that consists of minoxidil.

[0011] In order to prepare the hair restorer which blended the minoxidil like point \*\*, if it carries out from the point of the alternative absorption to hair papilla while it is more desirable to make pH into near neutrality, from the point of the stability in a solution, it needs to reconcile two technical problems that it is more desirable to make pH below into the acescence.

[0012] According to this invention, it is a hair restorer (if it is in aerosols, the component which does not contain propellants is meant.) about the loadings of a volatile solvent. Dissociation of the pH regulator blended with coincidence at the time of preservation of a hair restorer by carrying out to more than 50 V/V% [ being below the same ] can be controlled. Consequently, pH of the hair restorer at the time of preservation can be set near [ for preservation of the minoxidil / suitable ] neutrality and as the value preferably set to five or more pH, and can secure the preservation stability of the minoxidil.

[0013] On the other hand, after [ that ] the scalp is medicated with this hair restorer, the moisture which exists on the skin or in atmospheric air depending on that a volatile solvent vaporizes into atmospheric air promptly or the case is added, and dissociation of the pH regulator blended with the hair restorer progresses. consequently, the scalp which applied the hair restorer -- 4.8 or less suitable pH for the alternative absorption to the hair papilla of the minoxidil, the upper pH environment changes to 3.8 or less preferably, and its alternative absorptivity of the minoxidil improves.

[0014] In order to do so the effectiveness of this invention like the above, it is important to make a volatile solvent, water, the loadings of a pH regulator, especially the amount of a volatile solvent more than 50 V/V% of the whole hair restorer. If the loadings of a volatile solvent are less than this value, dissociation of a pH regulator cannot fully be controlled at the time of preservation of a hair restorer, but it is disadvantageous for maintenance of the preservation stability of a water-soluble drug.

[0015] As a volatile solvent which can be used by this invention, although a methanol, ethanol, propanol, isopropanol, etc. are mentioned, from a viewpoint of pharmaceutical-preparation-izing of a hair restorer, ethanol is the most desirable.

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PRIOR ART

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TECHNICAL PROBLEM

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[Problem(s) to be Solved by the Invention] However, since many of conventional absorption promotion components are oily components, such as myristic-acid isopropyl, the hair restorer which blended this tends to spoil a feeling of use, such as being easy to be sticky etc., and has a problem in the viewpoint of salability. Moreover, since it rides on a blood flow and shifts to the whole body, while absorptivity of minoxidil which permeated this appearance through keratin improves in the hair restorer using the conventional absorption promotion component, it is difficult for it, although an oily absorption promotion component has the effectiveness of making the minoxidil permeating into the skin through a horny layer to the scalp to make the minoxidil pile up.

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[0008] Therefore, while excelling in the absorption efficiency of the minoxidil which reaches the hair papilla of a hair bulb, in order to offer the hair restorer which can be satisfied also in preservation stability, it is required to design a hair restorer with which it is at the preservation and use time, and pH becomes respectively suitable by the device like pharmaceutical preparation.

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MEANS

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[Means for Solving the Problem] this invention persons are combining the volatile organic solvent more than the amount of specification, water, and a pH regulator, and completed a header and this invention for this technical problem being solvable.

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[0012] According to this invention, it is a hair restorer (if it is in aerosols, the component which does not contain propellants is meant.) about the loadings of a volatile solvent. Dissociation of the pH regulator blended with coincidence at the time of preservation of a hair restorer by carrying out to more than 50 V/V% [ being below the same ] can be controlled. Consequently, pH of the hair restorer at the time of preservation can be set near [ for preservation of the minoxidil / suitable ] neutrality and as the value preferably set to five or more pH, and can secure the preservation stability of the minoxidil.

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[0014] In order to do so the effectiveness of this invention like the above, it is important to make a volatile solvent, water, the loadings of a pH regulator, especially the amount of a volatile solvent more than 50 V/V% of the whole hair restorer. If the loadings of a volatile solvent are less than this value, dissociation of a pH regulator cannot fully be controlled at the time of preservation of a hair restorer, but it is disadvantageous for maintenance of the preservation stability of a water-soluble drug.

[0015] As a volatile solvent which can be used by this invention, although a methanol, ethanol, propanol, isopropanol, etc. are mentioned, from a viewpoint of pharmaceutical-preparation-izing of a hair restorer, ethanol is the most desirable.

[0016] Moreover, although the pH regulator which can be used by this invention has the desirable thing of fusibility to the mixture of water and a volatile solvent, if the safety and pH accommodation ability to the skin are taken into consideration, it will become suitable [ the pH regulator shown below ]. That is, they are an ascorbic acid, amino acid, ethylenediaminetetraacetic acid, a formic acid, a succinic acid, a citric acid, an acetic acid, oxalic acid, a tartaric acid, a nitric acid, a lactic acid, a fumaric acid, a maleic acid, a sulfuric acid, a hydrochloric acid, a malic acid, phosphoric acids, these salts, etc. Also in this, amino acid, ethylenediaminetetraacetic acid, a citric acid, an acetic acid, a nitric acid, a lactic acid, a sulfuric acid, phosphoric acids, and especially these salts are desirable.

[0017] Setting to this invention, the loadings of a pH regulator need to be the amount which can

demonstrate predetermined pH accommodation ability at the time of the administration to the skin etc. When the hair restorer before skin spreading is diluted with purified water 10 times, pH can determine the initial complement of this pH regulator simpler by determining that it becomes 3.8 or less preferably 4.8 or less. On the other hand, if the crystal of a modifier deposits on the skin after medicating the skin and it will also take into consideration that there is a possibility that a feeling of use may get worse, as for especially the loadings of the pH regulator in this invention, it is desirable to consider as 0.01 - 5 % of the weight 10 or less % of the weight to the whole hair restorer as a result. In addition, the loadings of the minoxidil in this invention should just specifically be 0.1 - 5 % of the weight per pharmaceutical preparation weight that what is necessary is just to consider as the general amount as a hair restorer.

[0018] If one sort chosen from the group which consists of the polyhydric alcohol of carbon numbers 2-8, a polyethylene glycol, or fatty acid ester, or two sorts or more are blended further in addition to the configuration of above-mentioned invention, the pH environment suitable for the alternative absorptivity of the suitable drug on the skin can be maintained for a long time.

[0019] As polyhydric alcohol of carbon numbers 2-8, a diethylene glycol, propylene glycol, 1, 3-butylene glycol, dipropylene glycol, a glycerol, a sorbitol, etc. are mentioned here. Moreover, the thing of a polyethylene glycol of molecular weight 200-600 is desirable.

[0020] Moreover, as ester, they are the ester (propylene glycol monoisostearate, glycerin monoisostearate, etc.) of lower alcohol, the ester (myristic-acid isopropyl etc.) of a fatty acid and polyhydric alcohol, and a fatty acid, and ester (deca glycerol monostearate etc. is mentioned.) of polyglycerin and a fatty acid. Especially, use of propylene glycol monoisostearate or glycerin monoisostearate is suitable.

[0021] What is necessary is just to make preferably the loadings of the polyhydric alcohol of these carbon numbers 2-8, a polyethylene glycol, or fatty acid ester into 5 - 20 % of the weight 0.5 to 40% of the weight to the whole hair restorer.

[0022]

[Embodiment of the Invention] The gestalt of the hair restorer of this invention can take a lotion, aerosol, or a tonic etc., and can prepare the pharmaceutical preparation approach by the general approach in pharmaceutical-preparation-izing of drugs or the charge of makeup.

[0023] Moreover, in this invention, various size enlargement components and addition components according to each gestalt can be blended in the range which does not spoil the effectiveness. As an usable addition component, cool-ized agents, such as gelling agents, such as emulsion stabilizer, such as surfactants, such as solubilizing agents, such as anti-oxidants, such as alcohol denaturant, such as denatonium benzoate, and dibutylhydroxytoluene, and a medium-chain-fatty-acid triglyceride, and a sorbitan fatty acid ester, and higher alcohol, and a water soluble polymer, and menthol, other binders, perfume, a color, etc. can be mentioned by this invention among such various components.

[0024] Moreover, blending active ingredients other than the minoxidil with the hair restorer of this invention does not interfere, either. As an usable active ingredient, vitamins, such as plant extracts, such as a sialid extract, and retinol acetate, can be mentioned by this invention.

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## EXAMPLE

[Example] Next, an example and the example of a trial are shown and this invention is explained still more concretely.

[0027] To <examples 1-3> minoxidil 1g, propylene glycol 10.4g, and ethanol 60.05g, various pH regulators were added, with purified water, the whole quantity was set to 100mL(s), the churning dissolution was carried out, and the lotion type hair restorer was prepared.

[0028] Thus, pH when diluting pH of the obtained hair restorer and this with purified water 10 times is measured, and it is shown in Table 1 with each presentation.

[0029] Moreover, the example of a comparison excluding a citric acid and ethanol from the example 3 was prepared according to the example 3.

[0030]

[Table 1]

[表 1]

成分名	実施例 1 (g)	実施例 2 (g)	実施例 3 (g)	比較例 (g)
ミノキシジル	1.0	1.0 minoxidil	1.0	1.0
BHT	0.05	0.05	0.05	0.05
プロピレングリコール	10.4	10.4 PG	10.4	10.4
水酸化ナトリウム	0.03	—	—	—
リン酸	0.55	—	—	—
乳酸	—	1.4	—	—
クエン酸	—	—	0.62	—
エタノール	60.05	60.05 ethanol	60.05	—
組成物の pH	5.0	5.0	5.2	8.3
投与後の pH	4.0	3.5	4.2	7.2

各実施例の組成物は、いずれも精製水で全量 100 mL に調製される。

[0031] <Example 4> minoxidil 1g, isopropyl methyl phenol 0.05g, 1,3-butanediol 9.42g, 0.5g [ of polyoxy ERIREN (20) hydrogenated castor oil ], and ethanol 70g, 0.55g of phosphoric acids, and 0.03g of sodium hydroxides were added, with purified water, the whole quantity was set to 100mL(s) and the churning dissolution was carried out. This liquid 50 weight section was put into the aerosol can, pressurization restoration of the wood ether 50 weight section was carried out, and the aerosol type hair restorer was prepared.

[0032] Carry out depilating of the abdomen of <example of trial> Wister system rat maleness (7 weeks old), and it fixes to the supine position under anesthesia. 40microl spreading of the lotions shown in the examples 1-3 and the example of a comparison of Table 1 is done to an abdominal fixed area (2cm<sup>2</sup>). After predetermined time amount (0 1 or 8 hours) neglect, decapitation of the rat was carried out, it was slaughtered, alcohol washed the lotion spreading section front face, the skin was extracted, transparence adhesive tape was strongly applied to the whole epidermis, and this was immersed in the hot bath tub of 60 degrees C of packages for 60 seconds on the food protection lap. After neglect cooling, the weight of



the skin (dermis) which removed the residual drug and the epidermis layer from the skin, and remained by removing a tape, and the amount of minoxidil in dermis were measured, and the amount of minoxidil per 1g of spreading section dermis (mg) was calculated. This result is shown in drawing 1.

[0033] The hair-papilla organization which is the growing point of hair exists in the dermic layer of the skin, and it is known that it is a target tissue for discovering the hair-fostering effectiveness of the minoxidil. From the result of an exam, the minoxidil of a twice [ about ] as many amount as this with which the pharmaceutical preparation of an example was detected in the example of a comparison about all the measuring times was detected in dermis.

[0034] This shows that the hair restorer of an example has sent the minoxidil of concentration higher than the example of a comparison around a hair-papilla organization.

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9

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**EFFECT OF THE INVENTION**

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[Effect of the Invention] This invention enables it to offer the hair restorer which is excellent in the alternative absorptivity to the hair papilla of the minoxidil at the time of administration to the scalp, securing the preservation stability of the minoxidil.

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**TECHNICAL FIELD**

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[Industrial Application] This invention relates to the hair restorer excellent in the preservation stability of the minoxidil, and the alternative absorptivity to woolen hair papilla.

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CLAIMS

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[Claim(s)]

[Claim 1] A volatile solvent 50 - 99 V/V%, water, a pH regulator, and the hair restorer that consists of minoxidil.

[Claim 2] The hair restorer according to claim 1 which is one sort as which a volatile solvent is chosen from ethyl alcohol and isopropyl alcohol, or two sorts.

[Claim 3] The hair restorer according to claim 1 which comes to blend one sort chosen from the group which furthermore consists of the polyhydric alcohol of carbon numbers 2-8, a polyethylene glycol, and fatty acid ester, or two sorts or more.

[Claim 4] The hair restorer according to claim 3 which is one sort chosen from the group which the polyhydric alcohol of carbon numbers 2-8 becomes from a diethylene glycol, propylene glycol, 1, 3-butylene glycol, dipropylene glycol, a glycerol, a sorbitol, and the polyethylene glycol of molecular weight 200-600, or two sorts or more.

[Claim 5] The hair restorer according to claim 3 which is one sort chosen from the group which fatty acid ester becomes from the ester of a lower alcohol fatty acid, polyhydric-alcohol fatty acid ester, and polyglyceryl fatty acid ester, or two sorts or more.

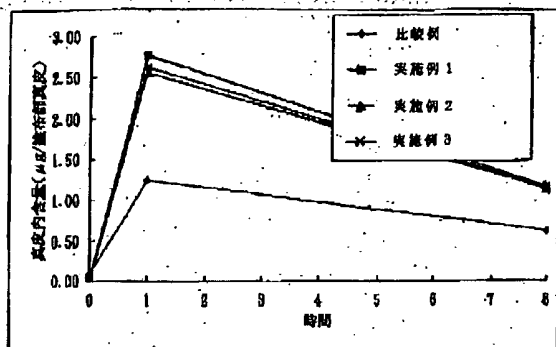
[Claim 6] A hair restorer given in either of claim 1 to claims 5 whose pH when diluting with purified water 10 times is 4.8 or less.

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Drawing selection drawing 1

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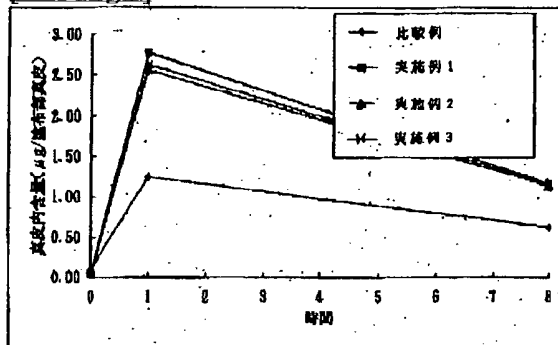
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DRAWINGS

[Drawing 1]



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